Modeling Cell-ECM Interaction

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***Short Abstract* —Tumor invasion is a multistage process that involves multiscale interactions between tumor cells and the extracellular matrix (ECM). Alignment of collagen fibers in tissue correlates strongly with tumor invasion, suggesting that reorganization of the dense matrix by tumor cells is involved in the invasive phenotype. Experimental studies indicate that excess collagen does promote both tumor formation and invasiveness; however how the collagen fibers are realigned by the interaction with growing and migrating cancer cells is unclear. We integrate *in vitro* and *in silico* studies of 3-D cell-ECM model and perform experimentally-parameterized simulations to investigate the cell-matrix interactions in tumor invasion.**

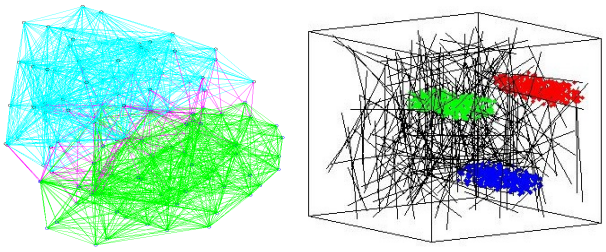
***Keywords* — cancer invasion, cell migration, cell-matrix interaction, extracellular matrix, mathematical model**

I. Introduction

THE cell-matrix interaction involves multiscale biomechanical processes, which are not easily accessible using the existing experimental techniques. We developed a mechanically realistic 3D cell-matrix model by investigating the deformation of both the cell and the ECM and the forces quantitatively to test how various properties affect the invasion of tumor cells. Tumor invasion is an emergent (nonlinear) outcome of the complex interactions between cells and ECM. A critical barrier to progress in the microenvironment field is the lack of computational and experimental tools to dissect this complexity. The mechanics of collagen fibers and networks have only recently been measured and modeled. We integrate experimental and modeling tools to contribute to the understanding of the biomechanical mechanisms of cell-matrix interactions, especially in the context of cancer invasion.

II. Results

We develop a 3D cell-ECM model to study the mechanical interactions between cell and ECM during cell migration, using the subcellular elements model [1]. In this model, each cell is a collection of subcellular elements; all elements interact through inter- and intra- cellular interaction potentials (Morse potential). The ECM is modeled as a network of interconnected elastic fibers; each fiber is a bead-spring chain. The interaction between the subcellular element and ECM bead follows a soft-core potential. The Figure 1 shows the cell representation and the cells embedded in a 3D collagen matrix. The cells pull on the fibers as they migrate through the 3D matrix.



a b

Figure 1: a) Two cells (red and cyan) modeled with subcellular elements; pink links specify the intercellular interactions. b) Three cells in a collagen network model (200x200x200 μm^3).

Experimental measurements of single cell migration on collagen gels (figure 2) demonstrate that cells migrate more slowly in dense compared to less dense 3D matrices (4 mg/ml compared to 1mg/ml collagen). When 1 mg/ml collagen matrices are pre-aligned, cell speed is not affected but directionality is increased.

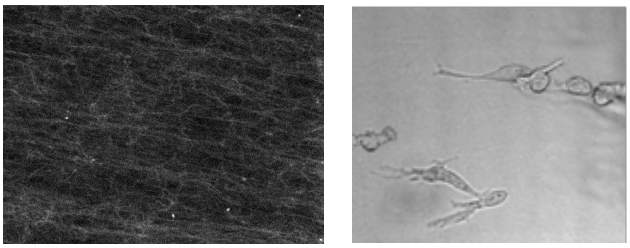


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Figure 2: Cell-ECM interaction *in vitro* [2]: a) Collagen structure imaged concurrently with cell migration. b) Light-microscopy image for single cell migration in 3D collagen.

Using parameters from experiments, our simulations show cell migration and ECM alignment dynamics compatible with experimental observations.

III. Conclusion

We have developed a biomechanical cell-matrix model. Integrated experimental and modeling study on ECM alignment due to cell migration show detailed dynamical changes within the neighborhood of cell-matrix binding sites. This model allows us to quantitatively and systematically uncover the mechanism of cell-matrix interaction in cancer cell migration and invasion.

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This work is funded by NIH NCI award: 1U01CA143069.

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